UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,234	04/07/2004	Ivan Labat	31280/42996	9734

4743 7590 07/10/2008

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
07/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,234	LABAT ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1,9 and 11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Invention II and SEQ ID NO: 1552 in the reply filed on 11/19/2007 is acknowledged.

Claim Objections

Claims 2-8 and 10 are objected to for reading on non-elected inventions. Correction is required.

Claims 3-8 are objected to for depending from claim 1 which is drawn to a non-elected invention. Correction is required.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claim s are directed. The title should reflect that the invention is directed to a diagnostic immunoassay.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require only a single, unspecified sample from a patient (claim 2) with an antibody to determine the level of the polypeptide of SEQ ID NO: 1552, and comparing that level to a "standard indicative of a higher risk of diagnosis of preeclampsia." There is no

guidance in the specification as to what such a standard is, nor how it is obtained, nor do the claims contain any details that would further elucidate the phrase. Accordingly, the claims are indefinite as it cannot be determined what such a standard is, nor what comparison is to be made, nor the meaning of the comparison, i.e. how it identifies a patient at higher risk of preeclampsia. Further, the claims are incomplete, as they do not comprise sufficient method steps to identify a patient as recited in the preamble of claim 2.

Claim 2 is further indefinite as it does not specify whether the patient is adult or fetus, nor whether, if the patient is an adult, that adult is pregnant.

Finally, claim 2 is indefinite because the preamble states that the method is "to identify a patient at higher risk of preeclampsia", whereas the claim concludes with a standard "indicative of a higher risk of *diagnosis* of preeclampsia."

Claim 10 is indefinite because there is no antecedent basis for "said proteins" in claim 2. Even if there were antecedent basis for such, it is not clear how the claim would further limit claim 2.

All remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 2-8 and 10 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:
1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention, as defined by the claims, is a diagnostic method to diagnose pre-eclampsia by doing an immunoassay for the protein of SEQ ID NO: 1552. The claims require only a single, unspecified sample from a patient (claim 2) with an antibody to determine the level of the polypeptide of SEQ ID NO: 1552, and comparing that level to a "standard indicative of a higher risk of diagnosis of preeclampsia."

At page 207 of the application, it is stated that:

A plurality of polynucleotide sequences were obtained from cDNA libraries obtained from both normal and pre-eclamptic placental tissues, using SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (for example, 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

As a cDNA library is generally generated from a single sample of cells, it is assumed, in the absence of any specific disclosure or evidence to the contrary, that the data represent the comparison of a single non-pre-eclamptic woman to a single pre-eclamptic woman, of non-specified states (it is not clear what the stage of pregnancy was, nor whether they were indeed at the same stage. It is further presumed that the libraries represent a single data point each, that is, were taken but once during the pregnancy, the timing of which is not disclosed.

The specification shows in the following table at page 139 of the PGPUB that the nucleic acid that encodes the protein of SEQ ID NO: 1552 (SEQ ID NO: 709) was upregulated in pre-eclamptic placenta vs. normal placenta. However, that upregulation was less than two-fold (19 vs. 10). That data was obtained using unidentified cDNA libraries (see preceeding paragraph). Protein was not measured. No other tissues or biological samples were measured. No measurements were made of serum, plasma, urine, cervicovaginal mucous, amniotic fluid nor fetal cells, nor it is disclosed what type of cell was isolated from the placenta.

The specification does not provide any guidance whatsoever as to how the "standard" of claim 2 is to be obtained, how it is to be compared to the test measurement, at what stage of pregnancy the measurements should be conducted, how many times the measurements should be repeated, etc. In fact, the art, as discussed below, teaches that the diagnostic method must compare samples taken from a single patient over time, not with a "standard indicative of a higher risk of diagnosis". Accordingly, the specification provides neither adequate written description nor enablement of the method of claim 2 for any patient nor any type of biological sample.

The specification correctly identifies the protein of SEQ ID NO: 1552 as being PP14, which has long been known in the art.

The prior art has recognized the protein of SEQ ID NO: 1552, most commonly called PP14, since at least the early 1980's, for example see Bolton et al., cited in the rejection under 35 U.S.C. §102(b), below. Bolton et al., Clinica Chimica Acta., 135:283-291 teach measurement of PP14, which is one and the same as SEQ ID NO: 1552, via radioimmunoassay, using antibodies generated in rabbits (see title, and page 284, 4th paragraph). In the abstract, it is stated that "Of seven patients with pre-eclampsia from whom two or more blood samples were taken, four showed increases in the concentration of (PP14) as pregnancy proceeded, compared with the normal pattern of decreasing values. At page 290, 3rd paragraph, it is disclosed that "Of the seven patients in which serial (two or more) samples were taken, four exhibited values which increased with gestation, in contrast to the downward trend in normal measurements."

Thus, Bolton et al. teach that there must be multiple measurements taken over time, and only looked at a correlation in maternal serum. They also found PP14 in amniotic fluid and unspecified extracts of placenta, see page 290, although it is not clear what types of cells may have been in the placental extracts. It is noted that the claims are also rejected under 35 U.S.C. §102(b) over Bolton. However, it is proper to reject claims under both 35 U.S.C. §102(b) and 112, first paragraph using the same reference when different interpretations apply to the claims. In the case of the art rejection, the broadest reasonable interpretation applies. However, in the case of this rejection, the Examiner is looking more to the specification to breathe life and meaning into the claims, and finds neither adequate written description nor enablement.

Jeschke et al., Virchows Archiv (Virchows Arch.) (Germany) April 1, 2005, 446/4

(360-368), who refers to PP14as glycodelin, disclose a study "to investigate the expression of glycodelin A (formerly named PP14) in decidual tissue of placentas with intrauterine growth restriction (IUGR), preeclamptic patients, hemolysis, elevated liver, low-platelet (HELLP) patients and normal decidual tissue. (see abstract). Note that placentas comprise multiple tissues, of which the decidual tissue is one. They performed immunoassays using monoclonal and polyclonal antibodies against PP14. Regarding decidual tissue, they teach at page 364 that "glycodelin expression was exclusively found in the decidua, whereas nostaining could be detected in the placental villi, neither in the trophoblast layer, nor in the villous stroma." Given this, and the fact that Jeschke et al. is published after the effective filing date of this application, it can be seen that it would require undue experimentation to determine which types of cells could be successfully used in the methods claimed. At page 365, first column, Jenschke et al. sate that "The expression of glycodelin A was significantly reduced in the decidual cells of all three types of pathological pregnancies investigated" (IUGR, pre-eclampsia, and HELLP). Accordingly, based upon the experiment therein, one could not differentiate pre-eclampsia from the other two type of pathological pregnancies examined. Accordingly, the specification does not enable one to distinguish pre-eclampsia from those other conditions. At page 367, Jeschke et al. teach that "in pre-eclamptic deciduas, only the expression of the glycodelin protein is significantly reduced, whereas the mRNA level is not." It is not clear how this affects the interpretation of the data in the instant specification, which do not measure protien, but find reduced mRNA (although, for reasons discussed above, the use of cDNA libraries vs. tissue samples, as is done by all cited references, renders the findings shaky, at the very least, and in need of substantial further experimentation to confirm.) Jeschke et al. also not that previous findings by Iino et al. and Howell et al., both made of record herein, were contradictory; Iino et al. found that PP14 levels decreased towards term in normal women, were higher than normal in women with gestational hypertension, but that the presence or absence of proteinuria, a necessary condition for diagnosis of pre-eclampsia, did not affect the results. On the contrary, Howell et al. found PP14 levels to be unaffected in patients with severe pre-eclampsia.

Another reference, Hass et al., 2003, gives a good definition of pre-eclampsia in the introduction, as being characterized by proetinuria, platelet aggregation, edema, and increased

vasoconstriction. Hass et al. found *no* significant differences in PP14 protein patterns in placenta when comparing normal to pre-eclamptic patients.

Finally, Gursoy et al. looked at leptin, another pre-eclampsia related protein, and found that while maternal concentrations were higher in the pre-eclamptic than control groups, no difference was found in fetal plasma leptin concentrations. This shows that one cannot predict from maternal results what the result will be for fetal tissues.

In view of the above, and that the claims do not specify type of tissue sample, what is to be compared, the specification provides no protein data for any tissue, the claims encompass all tissues, maternal and fetal, including serum, plasma, urine, cervicobaginal mucous, amniotic fluid and any other type of fetal cell, it would require undue experimentation to determine how to make and use the invention.

In summary, the claims contain insufficient method steps, and the claimed method is not sufficiently described in the specification in a way to allow person of ordinary skill in the art to practice the claimed invention. It is clear that there was no consensus in the art at the time the invention was made, that the specification does not compensate for the lack of teaching in the art, and that significant further experimentation was necessary to determine how to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bolton et al., Clinica Chimica Acta., 135:283-291.

Bolton et al. teach measurement of PP14, which is one and the same as SEQ ID NO: 1552, via radioimmunoassay, using antibodies generated in rabbits (see title, and page 284, 4th paragraph). In the abstract, it is stated that "Of seven patients with pre-eclampsia from whom

two or more blood samples were taken, four showed increases in the concentration of (PP14) as pregnancy proceeded, compared with the normal pattern of decreasing values. At page 290, 3rd paragraph, it is disclosed that "Of the seven patients in which serial (two or more) samples were taken, four exhibited values which increased with gestation, in contrast to the downward trend in normal measurements."

Thus, Bolton et al. disclose a diagnostic assay for pre-eclampsia using antibodies to SEQ ID NO: 1552, in which a decrease in protein levels in serial samples in the third trimester of pregnancy was shown to have a correlation with pre-eclampsia, and thus to be a diagnostic method. It is noted that diagnostic methods do not require 100% accuracy. Accordingly, the claims are anticipated.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
Primary Examiner
Art Unit 1647